Intradermal skin test results correlate with atopy

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Abstract

Intradermal skin testing (IDST) is performed by most allergists, but its value remains controversial. In most previous studies assessing the value of IDST, a positive result was based on a 5- to 6-mm wheal and erythema. While a subject's immediate reaction upon allergen exposure is a common endpoint to determine "allergy," additional known allergic phenomena such as the delayed or late-phase response to allergen exposure suggest that correlation only with current history or acute challenge may result in an incorrect labeling of false-positive results when, in fact, there is a physiologic response to exposure, albeit a reaction not immediately evident. We conducted a retrospective study to determine if positive IDST reactions represent nonspecific irritation or if they correlate with atopy. We retrospectively reviewed the records of 100 patients who had undergone skin prick testing (SPT) and IDST and compiled data on their age, sex, diagnosis, and number of skin and intradermal reactions. Results were analyzed according to a general linear model to see if the development of a positive IDST result correlated with atopy (defined as SPT positivity). We found statistically significant differences between SPT-positive and -negative patients with regard to diagnoses of asthma, rhinitis, or both (p = 0.008). Controlling for asthma and rhinitis, we also found a significant association between atopy and a positive IDST result; among atopic (SPT+) patients, a mean of 25.9% of IDST results were positive, compared with a rate of only 6.7% IDST positivity among the nonatopic (SPT–) patients (p < 0.0001). We conclude that IDST is more commonly positive in atopic (SPT+) than nonatopic (SPT–) patients, suggesting that a positive IDST represents genuine atopy and bona fide sensitization rather than nonspecific irritation.

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Introduction

A recent study by Oppenheimer and Nelson reported that 85.2% of allergists perform intradermal or intracutaneous skin testing.[1] In a subsequent and thorough review of intradermal skin testing (IDST), Calabria and Hagan concluded, "Most of the literature suggests that with a negative skin prick test (SPT) result, a positive IDST result adds little to the diagnostic evaluation of inhalant allergy."[2] In an even more recent commentary, Oppenheimer and Marshall, two well-respected authorities, observed, "The use of IDSTs adds little if any to SPTs when testing to potent allergens, such as cat and grass. In the case of less potent or unstandardized allergens, such as molds or trees, the addition of IDST may provide further utility."[3]

The purported lack of value of IDST seems to be at least partly explained by methods used to interpret the results. As Calabria and Hagan observed, "Definitions for a positive aeroallergen IDST result are variable, and evidence-based studies on grading of IDST results are lacking."[2] Virtually all research studies have classified IDST results as either *positive* or *negative* because such data are easier to work with. However, this system makes no distinction between small and large positive IDST responses as predictors of an allergen's contribution to a patient's allergic disease.

In an effort to explain the discordance between the apparent clinical utility of IDST, as reflected in its widespread popularity among allergists, and the results of investigational studies suggesting a lack of value, we undertook a retrospective review of patient charts. We sought to evaluate the relationship between reactivity to skin prick testing (SPT) and IDST in order to see if positive IDST results were random irritative events or correlated with atopy.

Patients and methods

We undertook a retrospective chart review of patients in a university hospital-based allergy and pulmonary medicine practice that treats primarily adults. A computer database search of procedure billing records from a single calendar year for a single physician (J.R.C.) was used to identify all patients who had undergone IDST as part of their clinical evaluation. A total of 406 patients were identified who had undergone a skin prick test; of these, 227 also had undergone at least one intradermal test. Most patients underwent SPT and IDST on the same day (9 were tested on different days). A group of 100 patients was randomly selected for this study.

All patients had undergone SPT with QUINTIP (Hollister-Stier Laboratories; Spokane, Wash.) and commercial reagents (Greer Laboratories; Lenoir, N.C.) at standard concentrations. Negative SPT controls were 0.9% saline with phenol 0.4% and human serum albumin 0.03% or glycerin 10.0%. The positive SPT control was histamine 10 mg/ml.

Most patients underwent SPT with 28 to 40 allergens using standard commercial extracts. SPT allergens included cat (10,000 BAU/ml), dog (1:20 w/v), dust mites (10,000 AU/ml), feather (1:20 w/v), dust (1:20 w/v), *Alternaria, Hormodendrum,* and pollens (all 1:20 w/v unless standardized extracts were available, in which case conventional SPT reagents were used) selected on the basis of their prevalence in the Philadelphia region.

The wheal and flare responses for each skin prick test were measured for each allergen control in its longest dimension and at 90°. IDST was not done for allergens that the physician considered positive by SPT. All skin test measurements were made by a single observer. This observer was aware of the SPT result when reading the IDST result. All skin testing was done in a clinical setting as part of routine care.

Patients with completely negative SPT results in whom allergy was still a consideration or in whom allergen immunotherapy was being contemplated underwent IDST to equivocal or negative antigens.

IDST controls were phenol saline with human serum albumin, and histamine 0.1 mg/ml (ALK-Abelló; Hørsholm, Denmark). IDST extract concentrations were tree, weed, dog, and mold (all 1:1,000 w/v), dust (1:100 w/v), cat (100 AU/ml), mite (*Dermatophagoides farinae* and *Dermatophagoides pteronyssinus;* 200 AU/ml), Bermuda grass (200 BAU/ml), and Kentucky/timothy grass (2,000 BAU/ml). Commercial treatment extracts (Greer Laboratories) were used and diluted in the practice to prepare the test solutions. A maximum of 28 IDST allergens plus controls were placed on any single patient.

Table 1. Criteria for defining skin test results

Negative—SPT or IDST results that were essentially the same as the negative controls.

Equivocal—SPT or IDST responses with (1) a diameter of erythema <3 mm more than the wheal for that allergen, (2) a wheal <3 mm more than the saline control, or (3) a faint flare.

Positive—a wheal ≥3 mm larger than the saline control and an area of erythema ≥3 mm more than the wheal for that allergen.

From the 100 charts randomly selected for detailed review, information was compiled on age, sex, diagnosis (asthma and/or rhinitis), and the number of positive SPT and IDST reactions. SPT or IDST results that were essentially the same as the negative control results were classified as *negative. Equivocal* SPT results were responses that appeared as (1) a diameter of erythema <3 mm more than its wheal, (2) a wheal <3 mm more than the saline control, or (3) a faint flare. All skin tests with a wheal ≥3 mm larger than the saline control and with an area of erythema ≥3 mm larger than its own wheal were classified as *positive* (table 1). Patients with at least one SPT+ reaction were deemed *atopic.*

Sample characteristics (age, sex, diagnosis) were calculated for the entire sample and by SPT status as *negative* or *positive.* Characteristics were compared across SPT status using the Pearson chi-square test for categorical variables and the Student *t* test for continuous variables. Square-root transformation was used to adjust the distribution of the percentage of positive IDST results to be more normal for further analyses. The square-root transformed percentage of positive IDST results was tested for association with SPT status according to a general linear model, controlling for characteristics that were found to be significantly associated with SPT status. All analyses were conducted on statistical software (version 9.1.3; SAS; Cary, N.C.).

The protocol was approved by the Institutional Review Board of Thomas Jefferson University.

Results

The 100-patient study group was made up of 64 women and 36 men (mean age: 43 ± 15.4 yr). Some 44% of patients undergoing IDST had no positive SPT result, and 56% had at least one positive SPT result. There were

Table 2. Distribution of age, sex, diagnosis, and IDST result according to SPT status

			n (%)				
		Mean age*	Sex*		Diagnosis†		
	n	yr (SD)	Women	Men	Asthma	Rhinitis	Both
SPT–	44	46 ± 16.0	32 (72.7)	12 (27.3)	7 (15.9)	24 (54.5)	13 (29.5)
SPT+	56	41 ± 14.7	32 (57.1)	24 (42.9)	5 (8.9)	17 (30.4)	34 (60.7)
Total	100	43 ± 15.4	64	36	12	41	47

** There were no statistically significant differences in SPT groups according to age (p = 0.124) and sex (p = 0.107).*
† Rhinitis alone was more common in the SPT– group, while combined asthma and rhinitis was more common in the SPT+ group (p = 0.008).

no significant differences in age and sex distribution according to SPT status (table 2).

Among the entire group, 12% had a clinical diagnosis of asthma, 41% had rhinitis, and 47% had both (table 2). Rhinitis alone was more common in the SPT– group than in the SPT+ group, while more of the SPT+ subjects had both asthma and rhinitis ($p = 0.008$). Since this was a retrospective study, that may reflect patient selection and referral patterns rather than bona fide differences between atopic and nonatopic patients seen for reactive upper and/or lower airways.

Using a general linear model and controlling for asthma, rhinitis, or both, we found a significant association between the percentage of IDST-positive results and atopic status, defined as a patient with at least one positive SPT result. Among SPT+ patients, a mean of 25.9% of IDST results were positive, compared with a rate of only 6.7% IDST positivity among the SPT– patients ($p < 0.0001$).

By contrast, no significant differences were seen between the atopic and nonatopic groups with respect to the control histamine and saline reactions. The mean IDST saline (wheal: 5.94 mm ± 1.40 for the SPT+ group vs. 6.24 mm ± 1.74 for the SPT– group; flare: 3.53 mm ± 3.91 for the SPT+ group vs. 2.84 mm ± 2.17 for the SPT– group) and histamine (wheal: 11.77 mm ± 2.12 for the SPT+ group vs. 12.35 mm ± 2.17 for the SPT– group; flare: 46.87 mm ± 11.80 for the SPT+ group vs. 41.76 mm ± 8.57 for the SPT– group) control reactions demonstrated no consistent difference in reaction size for the SPT+ compared with the SPT– patients. Indeed, the size of the saline wheal was greater in the nonatopic patients. This would suggest that the increased response rate to IDST in the atopic group reflected genuine allergic responses rather than nonspecific heightened skin responsiveness.

Discussion

The use of IDST has been criticized as adding "little to the diagnostic accuracy of skin tests,"[4] and numerous studies, as noted by Calabria and Hagan,[2] would at first glance seem to support that conclusion. But most studies divide skin tests into *positive* or *negative* without further quantitative interpretation, although quantitative scales are used for IgE levels, symptom scores, and lung function results in the very same articles.

Quantitative evaluations of IDST—for example, interpreting a 5- or 6-mm wheal differently from a 14-mm wheal, both of which are positive according to common criteria—are rarely done in most research studies that show reduced specificity. Our study did not directly address this issue, although we did use a more quantitative method to determine a positive result based on the patient's own skin reactivity—not just to saline and histamine but to the allergens themselves.

In vivo studies such as skin tests are measuring complex physiologic phenomena along a continuum.[5] Thus, interpretation based on characterizing IDST as either positive or negative may not be adequate in defining the optimal use of these tests. Little attention has been paid to studying patterns of responsiveness to see if IDST truly reflects atopy or just random irritative responses of little value, as critics suggest.

Most authors have attempted to correlate IDST results (be they positive or negative) with response to acute challenge or seasonal symptoms. While this methodology has demonstrated value in assessing results, as will be discussed, this usually accepted gold standard may be limited by contemporary understanding of the various ways that allergic sensitization may cause allergic disease, and it may result in inappropriately rejecting the utility of IDST.

We realize that in our data evaluation, we still used

characterizations of *positive* and *negative* in evaluating SPT results. However, this allowed us to make a correlation between atopy and the results of IDST. In effect, SPT reactivity was our gold standard for identifying patients who are allergic. We also used a definition of SPT positivity that varied depending on the patient's responsiveness.

Our study was a retrospective review of clinical data, which in most cases is a disadvantage. But our protocol may also more closely mirror the use of IDST in the population where it has the potential to be most helpful, defining the extent of allergy in patients where a more sensitive test for allergy is thought to be of clinical value.

In a frequently cited article, Nelson et al concluded that a positive timothy grass IDST result after a negative SPT result did not indicate "clinically significant sensitivity."[6] Those authors defined a positive IDST result as a 6-mm wheal with "definite erythema"; these criteria were less specific than ours. Only 9 of 68 subjects in their population (13.2%) were SPT– and IDST+ for timothy grass. Six of those 9 were SPT+ for common tree pollens. Nelson et al interpreted a decrease in symptom scores during the grass season to mean that IDST yielded false-positive results. An alternate and plausible explanation is that their patients' symptoms decreased as they went from the tree season (their baseline) to the grass season. They had fewer symptoms caused by grass allergens identified by just IDST, which might be expected if IDST reactivity was reflecting less intense allergy to those late spring allergens than to the tree allergens for which they were SPT+ and, at least plausibly, more "sensitive." This would not negate the positive IDST result if in fact a positive SPT reflects greater sensitivity with those pollen allergens. Rather, it would reflect the fact that SPT+ tree-allergic patients who are SPT–/IDST+ to grass have more trouble with tree allergy than with later grass pollen exposure.

It also suggests that evaluating seasonal allergic responses in SPT–/IDST+ patients would require the screening of perhaps an impractically large number of patients to find enough patients with the desired skin test pattern to study. Only 13% of the patients of Nelson et al fell into the SPT–/IDST+ category. It would require screening a large number of volunteers to produce a large enough study group to develop meaningful data for a prospective or challenge-based study.

The interpretation criteria used by Nelson et al[6] were similar to those used by Brown et al,[7] who classified an IDST result as positive if the wheal was >5 mm. While Brown et al used absolute cutoffs for interpreting IDST, they looked at serum IgE and radioallergosorbent test (RAST) scores in a more quantitative way. They found that the serum IgE level was greatest in all patient categories in the IDST+ group, although the differences were not statistically significant.

Sharma et al examined laboratory workers exposed to mouse protein, and performed IDST, SPT, and serum IgE antibody measurements followed by nasal challenge.[8] They found that none of the subjects with a negative IDST result had a positive challenge, but that 5 of 15 patients with a positive IDST result and a negative SPT result had a positive challenge. They defined a positive IDST result as a reaction 3 mm greater than the negative control, noting that SPT–/IDST+ subjects had a higher threshold for reacting to the nasal antigen. As with our results, this suggests that a positive IDST result is not just a random phenomenon, and that skin sensitivity may correlate with airway sensitivity, albeit to a lesser degree than what is demonstrated with SPT.

McCann and Ownby observed, "Allergy skin testing for immediate hypersensitivity…is subject to multiple variables that can affect the result. Some of these are patient dependent, such as the patient's age, underlying skin condition, or use of medications that can interfere with the test results."[9] They noted better intraobserver reproducibility in the interpretation of SPT with more strongly positive results, and found "marked agreement on strongly positive and negative tests and more disagreement on test items in between." Experience suggests the same may hold true for IDST that can also help clarify equivocal SPT+ results due to larger IDST reactions if allergy is indeed present, but confirmation of that hypothesis is beyond the scope of our data.

Most authors have attempted to correlate skin test positivity with either current allergy or inhalation challenge. However, there are additional limitations in correlating IDST results with either current allergy or inhalation challenge in determining the absolute reliability of intracutaneous tests.

Hagy and Settipane demonstrated several decades ago that skin-test–negative college students had a lower incidence of developing an allergic disease in subsequent years than did their equally asymptomatic but skin-test–positive contemporaries.[10] In retrospect, those "false positives" were in actuality true positives. Could the same early sensitization effect apply to IDST?

Frenz reviewed the complex relationship between pollen counts and symptoms, including the number of days of demonstrated delay in the onset of symptoms

after pollen counts increase and the effect of previous exposures in heightening hypersensitivity to subsequent exposure.[11] In effect, those patients responded to exposure to allergens, but over a period of days, a much longer observation period than customary inhalation challenge evaluations that are held out as the gold standard in evaluating the utility of IDST.

Using SPT, others have shown a correlation between increased sensitization to environmental allergens and heightened nonspecific airway responsiveness in adults[12,13] and children.[14] Most of the child responders had no history of asthma or wheezing. Those would have been called false-positive results if current asthma were the standard for declaring an IDST result a true positive.

Taken together, these studies suggest that reaction to challenge or even current symptoms may not correlate adequately with atopy to allow them to be used as absolute standards for defining true positivity in evaluating the specificity and sensitivity of either SPT or IDST. In clinical practice, the development of increased airway reactivity over time may correlate most closely with the effect of allergens on the development of allergic disease. Such studies, however, are virtually impossible to do because it would be impractical to totally control the exposure of patients over the weeks or months that would correlate with the exposure patients experience naturally that results in heightened nonspecific reactivity.

Wood and colleagues performed a qualitative allergen inhalation challenge and found no significant difference between their IDST+ and IDST– groups.[15] They also used a cutoff of ≥6 mm for calling an IDST result positive, although they used a graded scale for symptom scores and changes in forced expiratory volume in 1 second (FEV_1). The IDST+ group had higher symptom scores, although the difference between groups did not reach a level of clinical significance. Also, Wood et al studied their patients for 1 hour, which is not long enough to detect late-phase reactions or increased airway responsiveness. Late-phase reactions have been shown to occur in animal and other allergies.[16]

Conventional inhalant allergy patients often respond to multiple allergens. Unlike the case of a patient who can be removed from exposure to workplace allergens, avoidance of all environmental allergens is impractical. Limitation of a patient's exposure to the actual laboratory challenge is not feasible in conventional seasonal, dust mite, or dander allergy in contrast to occupational allergy models. That makes challenge with one common environmental antigen in isolation further problematic as a gold standard, and it may explain some previous results.

Conclusion

Allergy diagnosis requires a combination of history, physical examination, and appropriately used diagnostic studies.[17] According to current immunotherapy practice parameters, "The selection of the components of an allergen immunotherapy extract that are most likely to be effective should be based on a careful history of relevant symptoms with knowledge of possible environmental exposures and correlation with specific test results for IgE antibodies."[18] The authors of these guidelines recommend against the "remote practice of allergy," which involves interpretation of specific antibody measurements without correlation with the history and other findings.

We have demonstrated that IDST positivity correlates with the atopic state rather than representing random irritation. We speculate that quantitative interpretation of IDST, correlated with the history, is the optimal use for these tests, adjusted for the effect interpretation will have on management. For example, a higher degree of certainty may be appropriate in suggesting immunotherapy than in prescribing mattress encasements or including an additional antigen when immunotherapy is already planned based on SPT results.

Söderström and colleagues evaluated a more quantitative approach to specific IgE interpretation and concluded, "Using the quantitative level of IgE antibody to an allergen increases the utility of the information in clinical context compared with a qualitative statement of whether IgE is present or not."[19] Lemon-Mulé et al[20] and others have used IgE levels and SPT responses to create predicted probabilities of positive ingestion challenge reactions—the larger the reaction, the more likely a response. There is no reason to believe the same does not hold true for IDST size, as well. Unfortunately, the literature evaluating the validity of IDST has not taken that approach, using arbitrary designations of positive and negative instead.

Indeed, newer recommendations are to measure the longest diameter of the wheal and corresponding flare in reporting results.[21] Ignoring such quantitative data in favor of interpretations of positive and negative in older studies defeats the purpose of reporting wheal and flare measurements and seems likely to be at least partly responsible for the differences between everyday allergy practice and investigational findings of poor specificity for IDST. This was a limitation of our study, as well,

because in order to analyze our data, we characterized SPT and IDST results as *positive* or *negative,* although we also considered some results *equivocal.*

Analysis of reaction size for various allergens, histamine, and saline is under way to better characterize these findings, including the size distribution of intradermal responses as it relates to different types of antigens. Still, we have demonstrated that response rates to IDST are greater in atopic patients, suggesting that IDST is detecting bona fide allergy rather than an insignificant irritant effect. This finding appears to support allergists' selective use of IDST in clinical practice. More work needs to be done to establish the role of IDST in the evaluation and treatment of allergic sensitization and inhalant allergen-related disease.

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